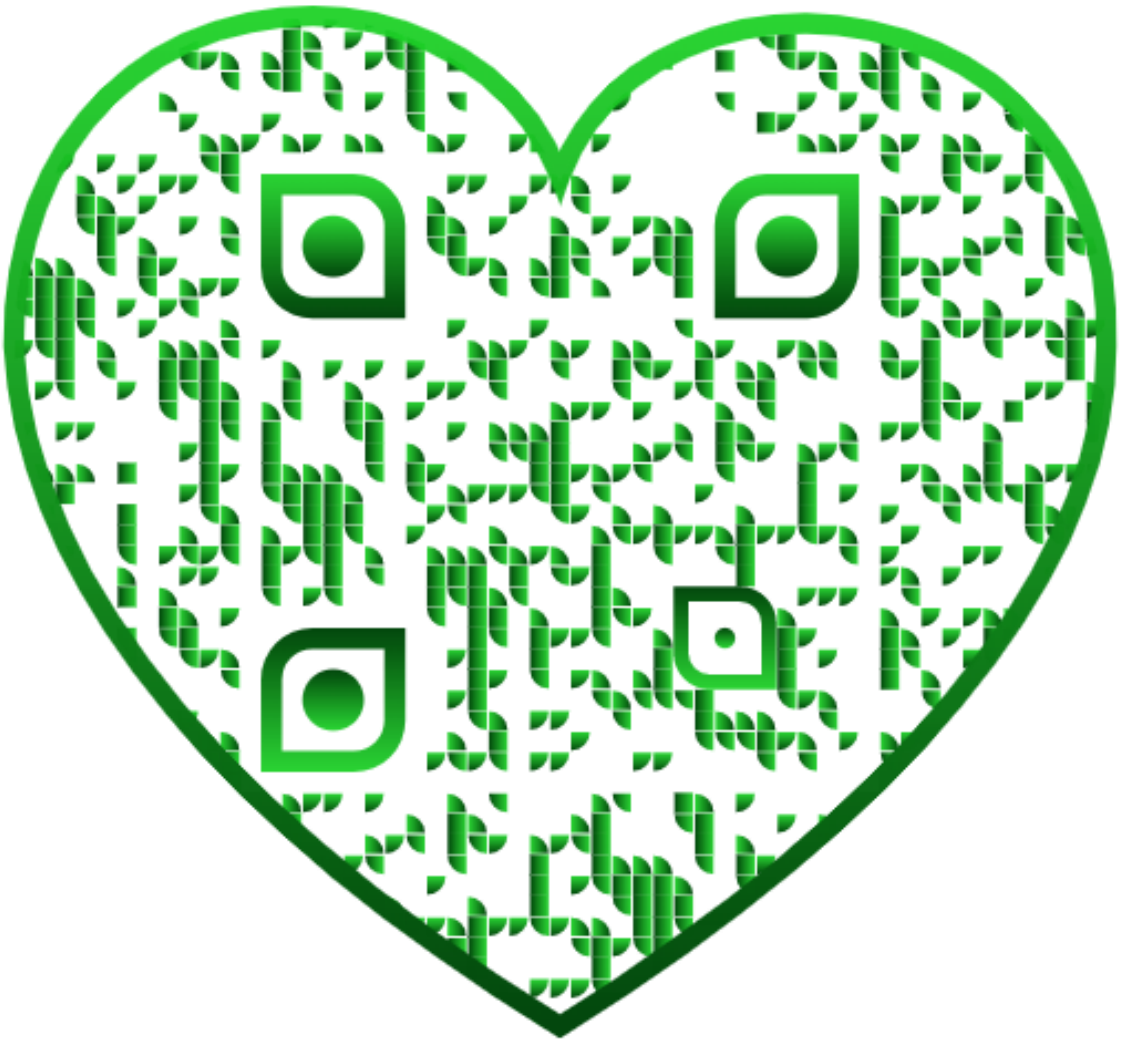
8. Incompatibilities in Formulation



Introduction

- **Incompatibility** ~ a condition where two or more agents when brought into contact result in a chemical decomposition, physical disassociation, or therapeutic opposition.

- Incompatibles are

  - Substances which have opposite medicinal properties, or

  - Substances when mixed together, react chemically and/or physically to produce other substances.

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- Incompatibility can be detected by changes in physical, chemical, or therapeutic qualities.
- An understanding of incompatibilities can save the pharmacists' valuable time in compounding as well as ensure the therapeutic efficiency of the products.
- Incompatibilities range from minor to dangerous.
  - These may affect Safety, Efficacy, and Appearance of pharmaceutical products.

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- The Pharmacist's knowledge of the pharmaceutical, chemical and pharmacological background is very important to:
  - Anticipate incompatibility, and
  - Decide the most appropriate action to be taken
- Whenever two or more single drugs, official preparations, or proprietary products are ordered on the same prescription, the pharmacist should confirm that there is no incompatibility.

- Incompatibility problems are categorized either into:

1. Physical incompatibility
2. Chemical incompatibility
3. Therapeutic incompatibility

Physical incompatibilities

- These are often called pharmaceutical incompatibility and are **evidenced** by the failure of the drugs to combine properly.

- These incompatibilities produce a mixture which is unacceptable in appearance and taste and may result in non-uniform dosage form.

  - This may result in difficulties in accurate dosing, which will in turn affect therapeutic activity.

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- The changes which occurs as a result of physical incompatibility are usually **visible** and can be easily corrected by applying the pharmaceutical **skills**.
- Physical incompatibilities may lead to change in color, odor, taste, viscosity and morphology.
- Physical incompatibilities may be due to:
  - Immiscibility
  - Insolubility or
  - Liquefaction of components of the mixture

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Immiscibility

- This manifestation appears clearly in emulsion, creams, lotions, and some types of ointments.
- Separation into two phases is noticed in these pharmaceutical dosage forms.

- The following factors lead to immiscibility:
  - Incomplete mixing
  - Addition of surfactant with:
    - Unsuitable concentration
    - False time of addition
    - Unsuitable for the type of emulsion

- Presence of microorganisms
  - Some bacteria grow on constituents of mixture
  - Produce enzymes which oxidize the surfactant
- Temperature
  - Storage must be in room temperature to prevent separation

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- Immiscibility will occur when:
  - Oils are mixed with water,
  - Concentrated hydro-alcoholic solutions of volatile oils mixed with aqueous preparation,
  - Addition of high concentration of electrolyte to a saturated aqueous solution of a volatile oil.

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Insolubility

- The major of incompatibilities here are due to insolubility of the inorganic/organic compounds in a particular solvent.
- **Factors** that may affect solubility include: Change in pH, Milling, Surfactant, Chemical reaction, Complex formation, and Co-solvent.
- Consider the following issues,

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- Preparations containing indifusible solids - need thickening/suspending agents
- Poorly wettable solids - need wetting agents
- Preparations containing potent insoluble drugs - a soluble derivative of the drug may be substituted
- Constituents of alcoholic vegetable extracts - may precipitate when solvent is changed
- Excessive SSAs - will cause claying

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- Dispersions of hydrophilic colloids - may be precipitated by high concentration of alcohol.
- High concentration of electrolytes in emulsions - may cause salting out.
  - High concentration of electrolytes cause cracking of soap emulsions.

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Liquefaction

- When certain low melting point solids are powdered together, a liquid or soft mass known as "eutectic mixture" is produced.
  - This occurs due to the lowering of the melting point of mixture to below room temperature and liberation of water of hydration.
  - E.g. Any pair of Camphor, Menthol, Phenol, Thymol, and Chloral Hydrate.

Chemical incompatibilities

- Chemical incompatibilities often occur due to oxidation-reduction, acid-base hydrolysis or combination reaction.
- These reactions may be noticed by precipitation, effervescences, decomposition, color change or by explosion.
- Two types: Tolerated or Adjusted

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- Tolerated:
  - The chemical interaction can be minimized by **changing** the order of mixing or mixing the solutions in dilute forms but **no alteration** is made in the formulation.
- Adjusted:
  - The chemical interaction can be prevented by **addition or substitution** of one of the reacting ingredients of a prescription with another of equal therapeutic value.

- Chemical incompatibilities may be caused by:

    1. pH change
    2. Double decomposition
    3. Complex formation

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pH Change

- Most medicaments are salts of weak acids or weak bases,
  - These salts are soluble in water, however, the unionized acids and bases practically insoluble.
  - If a salt of a weakly basic drug is made alkaline, the free base may be precipitated, and vice versa.

- Whether precipitation occurs or not depends on:
  - Solubility of the unionized acid/base,
  - pH of the solution,
  - Dissociation constants.

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Double Decomposition

- Precipitation of Alkaloids and Alkaloidal salts by hydroxides, carbonates, iodine, iodides, bromides, borates, or tannic acid.
- Barbiturates with Ammonium Bromide.
- Potassium chlorate with oxidative substances
- Soluble salicylates with acids or with alkali barbiturates
- Cationic and Anionic compounds of high molecular weight
- Soap emulsions and Polyvalent Cations

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Complex Formation

- Medicaments or preservatives may bound to macromolecules present in the formulation.
  - Because the complexes are too large to penetrate cell membrane, the activity of the medicament and preservatives may be reduced.
  - This problem is common with non-ionic macromolecules.

- Complex formation may be reversible
  - When unbound drug in the preparation has been utilized it is replaced from the complex.
  - Complexation may be used as a method of depot therapy.
  - Complexation may reduce irritancy and improve stability.

Therapeutic incompatibilities

- Such incompatibilities exist when the response to drug(s) is of different nature or intensity than that intended.
- Some combination of drugs and diet may be dangerous.
  - When circumstances produce a feeling of doubt on the part of the pharmacist, the prescribing physician should be advised.
  - The pharmacist must be watchful for unintended therapeutic interactions and should provide themselves with helpful sources of information.

- Therapeutic incompatibility may result from:
  - Synergistic combination
  - Additive combination
  - Potentiation combination
  - Antagonistic combinations
  - Contraindications

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Synergistic combination

- When certain drugs having the **same** pharmacologic action are prescribed together, the combined action they produce is greater than the sum of their individual actions.
- Such combinations should be in reduced amount.
- The synergistic action will sometimes be desired to decrease toxicity or reduce cost of prescription.

- Examples
  - Combinations of sulfonamides show less nephrotoxicity than a single sulfonamide.
  - Neomycin + erythromycin combination has a broader spectrum than either antibiotic alone.
  - Aspirin + codeine combination reduces the amount of expensive codeine required.

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Additive combinations

- Occurs when two or more drugs having the **same** effect are combined and the result is the sum of the individual effects relative to the doses used.

- Examples

  - Benzodiazepines + alcohol (adding effect)

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Potentiation combinations

- Describes a particular type of synergistic effect, drug interaction in which only one of two drugs exerts the action that is made greater by the presence of the second drug.

- Examples

  - Caffeine + Ergotamine (Cafergot preparation) ~ Potentiation of the effect of ergotamine by the presence of caffeine

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Antagonistic combinations

- Drugs having **opposite** pharmacological action are prescribed together, their actions cancel each other.
- Examples
  - Stimulants with sedatives (hypnotics) e.g. caffeine with chloral hydrate.
  - Purgatives with antidiarrheals e.g. MgSO4 with tannins
  - Acidifiers with alkalinizers e.g. Aspirin with AL(OH)3.

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Contraindications

- Are drugs when prescribed together may lead to increased toxicity or decrease activity.
- Examples
  - Tetracycline is contraindicated with any drug containing Ca^{2+} ions as it form non-absorbable complex.
  - Inactivation of sulfa drugs by procaine HCl.

Corrective Measures

- Addition of an ingredient that does not alter the therapeutic value.
- Change of an ingredient, or change of the order of mixing
- Change of a solvent.
- The utilization of special techniques in compounding, such as treating each ingredient separately.
- Omission of an agent that has no therapeutic value, or that may be dispensed separately.

Intentional incompatibilities

- Examples
  - Tincture myrh is diluted with water to give a precipitate which is used as a gargle in the treatment of tonsillitis.
  - Central nervous system stimulants may be used to overcome the drowsiness produced by anti-histaminic drugs.
  - A mild laxative antacid such as Mg(OH)2 may be used to overcome the constipating effect of an astringent antacid such as AL(OH)3.
  - Strong iodine solution U.S.P. (Lugol's solution)